C. *Does "Mixing" Mean Adding*?

TLC also contends Vestar is incorrectly reading the term "mixing" as if it meant "adding." It notes that the authors of the patent distinguished between adding and mixing in Example 1 of the specification when they refer to the hydrophilic compound as "added and then thoroughly mixed."

Vestar looks to this same example in the specifications to support its contention that the claim should be read as describing a process where the hydrophilic compound is mixed with liposomes by adding it to the colloidal dispersion. Example 1 reads:

> A liposome dispersion in water was prepared which comprised 25 mg of lecithin per ml of dispersion; the encapsulated solution was 100 mg/ml aqueous insulin solution. Dextran (Pharmacia T-70) (25 mg/ml) was added as a stabilizer to the liposome dispersion and was thoroughly mixed therein.

Vestar contends that this example confirms that the claim language sets forth a process which "comprises mixing a hydrophilic compound with the colloidal dispersion of the liposomes" and describes adding a hydrophilic compound and mixing it with existing liposomes. Vestar argues this is significant because under this process of adding and mixing, the hydrophilic compound is present only on the outside of the liposomes. Schneider stated in his patent that by adding sugar to the outside he was only able to retain sixty-five to seventy-five percent of the contents of the liposomes, a number Vestar contends is pharmaceutically unacceptable.

D. *TLC's Prior Inconsistent Reading of the Word "Mixing" in the Patent*

Vestar contends that prior to filing this action, TLC had read the claim language as describing the addition of the hydrophilic compound to liposomes and not as describing the formation of liposomes by mixing them with the compound. Vestar points to Dr. Ostro's November 1988 letter to Philip Schein and TLC's arguments before the European Patent Office in support of the Janoff patent as evidence of this prior interpretation.

In his November 1988 letter, Dr. Ostro wrote: "You will notice in Claim #1 of the Battelle patent that the authors added the hydrophilic compound to the outside of the liposomes and do not include it in the formation process. Therefore, no sugar will be on the inside of the liposomes."

In his October 8, 1990, letter to the European Patent Office, TLC's counsel wrote:

> Schneider . . . teaches the dehydration of liposomes by mixing a liposome dispersion with a sugar and then drying the preparation.
>
> In contrast, [Janoff's] claim 1 is directed to the preparation of liposomes in the presence of a protective sugar, then dehydrating the preparation. In [Janoff's] preparation, the liposomes contain the protective sugar on BOTH SIDES of the lipid bilayers ("*preparing* a liposome which includes . . . sugars . . ."); as contrasted with the Schneider patent which contains sugar on only the exterior of the liposomes.

Vestar argues the court should find TLC is estopped from obtaining relief in this case based on the new (and inconsistent) reading of the claims it alleges TLC has presented to this court. There is some authority, under the doctrine of "judicial estoppel," for the proposition that courts will find a party is estopped from obtaining relief based on alternative and inconsistent positions taken in litigation. *Allen v. Zurich Ins. Co.*, 667 F.2d 1162, 1166 (4th Cir. 1982). Thus, in *Allen* 667 F.2d at 1166, the court stated, "in certain circumstances a party may properly be precluded as a matter of law from adopting a legal position in conflict with one earlier taken in the same or related litigation." The court explained that judicial estoppel is applied in these circumstances to "prevent the party from 'playing fast and loose' with the courts, and to protect the essential integrity of the judicial process." *Id.* The cases recognize, however, that a patent owner will not be precluded from taking inconsistent positions in litigation unless the party opposing the subsequent position demonstrates either personal reliance on a decision granted in the prior suit, prejudice in the current litigation by reason of the prior decision, or the patent holder's apparent misuse of the court. *Hybritech Inc. v. Abbott Lab.*, 849 F.2d 1446, 1453-54 [7 USPQ2d 1191] (Fed. Cir. 1988). Vestar can not meet these standards in this case.

Vestar's better argument on the significance of Ostro's letter and the statements before the European Patent Office is that they are relevant as evidence of how TLC had in fact read the words of the claim at a time when it was not looking at them as a necessary step in building a claim for relief that moves from complaint to recovery. TLC's prior statements are also relevant as they are some evidence of how one skilled in the art would read the words in the patent.

E. *The Meaning of the Claim Language "Mixing a Hydrophilic Compound with the Colloidal Dispersion of the Liposomes"*

For the following reasons, the court finds the words in claim 1 and 11 do not describe

Vestar's process used to make AmBisome. First, the words in the claim, "mixing a hydrophilic compound with the colloidal dispersion of the liposomes," describe a compound that is mixed with existing liposomes, not with lipids that will form liposomes. These words appear to be relatively simple and straight-forward. In addition, the evidence presented provides no basis for believing that Schneider intended a meaning different from the ordinary meaning of these words as they would be understood by one skilled in the art. In fact, there is no evidence in the record to suggest that at the time the language for the claim was drafted, or at the time they made their discovery, Schneider and Lamy expected or intended that the compound could or should be mixed in when the liposomes were being formed. Thus, there is nothing in the record to suggest they intended the words in the claim to cover more than a process in which the compound is mixed or added with liposomes that have already been formed.

Second, the specification provides further support for this interpretation. Both Examples 1 ("[d]extran . . . was added . . . to the liposome dispersion") and 2 ("dextran was replaced by an equal weight of gum arabic as stabilizer") refer to "mixing a hydrophilic compound with liposomes."

Third, TLC's prior statements describing the claim provide further evidence that the words can and should be read to mean adding a compound to existing liposomes.

Finally, even if the court assumes for the purpose of its infringement analysis that Dr. Schneider's invention was as Dr. Cullis' described — mixing a hydrophilic compound with a liposome dispersion prior to lyophilization (and as will be discussed below, that may not have been his invention) — nevertheless, the words Dr. Schneider selected to claim his invention do not describe that process. If that was his invention, he claimed less than he discovered.

F. *Conclusion as to Literal Infringement*

[1] In summary, the court finds that as used in claims 1 and 11 of the patent, the words "a process . . . which comprises mixing a hydrophilic compound with the colloidal dispersion of liposomes" should be construed to mean mixing a hydrophilic compound with an existing liposome dispersion. As Vestar does not mix a hydrophilic compound with an existing liposome dispersion in the process it follows in making AmBisome, it does not infringe claim 1 or 11 of the '360 patent. In addition, because Vestar does not infringe the independent claims 1 and 11, as a matter of law it cannot infringe claims 2, 3, 4, 12, 13 and 14, which depend on claims 1 and 11.

III. *Is the '360 Patent Invalid or Unenforceable?*

Vestar has counterclaimed for a declaratory judgment that the Schneider patent is invalid and unenforceable, contending that the patent was fully anticipated by the Racker article, the invention would have been obvious to one of ordinary skill in the art, the patent lacks enablement in that it fails to disclose the hydrophilic compound that will work in the process, and that TLC obtained the patent through inequitable conduct by misleading the examiner about the meaning and significance of the Racker article.

Under 35 U.S.C. § 282, United States patents are presumed valid. One challenging the validity or enforceability of an issued patent must prove these defenses or claims for relief by clear and convincing evidence. *Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1423 [8 USPQ2d 1323] (Fed. Cir. 1988). When prior art or other evidence is presented at trial which was not considered by the PTO, a court need not accord deference to the PTO's determination of validity when undertaking its own independent review. *American Hoist & Derrick Co. v. Sowa & Sons Inc.*, 725 F.2d 1350, 1359-60 [220 USPQ 763] (Fed. Cir.), *cert. denied*, 469 U.S. 821 [224 USPQ 520] (1984).

A. *Additional Facts and Opinions Relevant to Invalidity and Inequitable Conduct*

Set forth below is a brief review of additional evidence relevant to these issues.

1. *Dr. Schneider's invention*

Dr. Schneider began working with liposomes at Battelle in the early 1970s. In 1975 he turned his research efforts to using liposomes as drug delivery devices. One problem he identified and sought to solve was how to prepare liposomes for pharmaceutical purposes that would be sufficiently stable so as to have a shelf life of at least several months. At trial, he described the problem as follows:

> And pharmaceutically, you have a product which is stable at least several months and preferably several years. Now, liposomes have a number of — of problems in relation to this.
> * * *
> As we — as we said earlier, if you think about his soap bubble analogy, they have this very thin membrane which may rupture and which may release the content. So you have the stability issue already there.
> Then you have a second problem which may occur is that the membrane doesn't

rupture, but your compound which is inside, in the aqueous phase, may gradually leak out in the medium.

And after several weeks, you end up with all your drug — not any more inside, but in the external phase which is what you don't want to have.

You have a third problem, which is the hydrolysis of phospholipids. It was known that phospholipids, when they are in an aqueous environment, tend to hydrolyze and they lose one of their fatty acid residues, which is one of these hydrophobic tails. They lose one of them and are transformed in lyso derivatives. And these lyso derivatives are not capable of forming bilayers and, on the contrary, they are detergents. They are destroying bilayers.

Dr. Schneider testified that he decided to investigate hydration as a stabilization method:

I thought that dehydration would be the best technique, because it solved all the stability issues which I mentioned earlier on the hydrolysis of phospholipids, the release of the entrapped drug, and the structural modification of the membranes, also.

* * *

The basic idea was that when you dehydrate liposomes, when you remove water, they will gradually come together, they will fuse, one into the other. And you will be ending up with a film of phospholipids on the bottom of your vessel.

* * *

Now, the dehydration per se doesn't function. It is not really surprising, because if I just come back a minute to what I explained about the Bangham procedure, you first make a film of phospholipids that you hydrate, and you make liposomes. If you remove the water, you are going backwards, and you end up with film of phospholipids on your glass vessel again. But you lose your liposomes.

Dr. Schneider described how he solved this problem:

So what I thought is that maybe I should find something which could go in between these liposomes. And it could avoid that they fuse one to the other, which separates them out.

And I was thinking about macro molecules. I though they would probably be able to stick some out to the external part of the liposomes, and stabilize it, and avoid, also, the breakdown of these membranes.

And I thought one should add probably quite a large quantity of it, to have really a lot of space between the liposomes when we dehydrate, and I did the experiment, and it worked beautifully the first time. It was a surprise. And it was a great joy as a scientist to see that sometimes hypotheses work.

On cross examination, he testified:

Q: Now, when you tried to lyophilize liposomes, or I should say, when you lyophilized liposomes, you used a standard lyophilization procedure.

A: Yes.

Q: You determined that lyophilization procedure more or less by chance?

A: Yes.

Q: And you didn't do a literature search on lyophilization either, did you?

A: No. I think we discussed this matter. To me it seemed that the subject I was on was so different from everything else I had heard.

* * *

Q: And you used a procedure that you came upon by chance?

A: It's a procedure which was currently used in the laboratories I was in.

Q: And you felt that the lyophilization procedure was very simple?

A: Yes.

Q: And that there was nobody particularly experienced in lyophilization at Battelle for you to go to talk to?

A: No.

Q: And you just used standard lyophilization equipment at Battelle?

A: Yes.

* * *

Q: Now, in determining what molecules to use, you went to a book in the Battelle Lab. Right?

* * *

A: Once I had done these experiments, I was faced with the question to know if other components were likely to do this. And so, in the book, like the ones which I gave you just recently, I looked at other macro molecules which are currently used in the field of biochemistry. And I found dextran and gum arabic and many others.

Dr. Schneider described his invention as follows:

The inventive step was to find that by adding a hydrophilic agent, such as macro molecules, you could prevent this fusion, and you could thus obtain a powder, which after reconstitution gave again the liposomes.

2. *Expert testimony on lyophilization*

In support of its affirmative defenses and counterclaim, Vestar offered the testimony of Stephen L. Nail, Associate Professor in the School of Pharmacy at Purdue Universi-

ty. Dr. Nail is a 1972 graduate of Purdue, with a Bachelor of Science in Chemical Engineering. He received a doctorate in 1975 from Purdue's School of Pharmacy and Pharmacal Sciences. His primary interest is physical chemistry and freezing and freeze-drying. He teaches a course in the graduate program at Purdue in advanced pharmaceutical manufacturing, that includes teaching on the role of protective agents, both cryoprotectants and lyoprotectants, in connection with the formulation and processing of injectable dosage forms of pharmaceuticals. He has written on the subject of the physical chemistry of freezing and freeze-drying.

Dr. Nail testified that he had reviewed scientific literature in an effort to determine the state of knowledge in freeze-dried science and technology in 1977 and before, and it is his opinion that someone knowledgeable in the field prior to 1977 would certainly be expected to know about the need for protective agents and have access to prior experience with analogous membranous-type structures to know what kinds of compounds would be expected to be effective. In support of his opinion, he referred to an April 1974 article by Betty J. Marshall and others in *Applied Microbiology*, entitled "Some Factors Affecting the Viability of Dried Bacteria During Storage in Vacuo." In the paper, the authors discuss improvements in the viability of two types of microorganisms after they are freeze-dried in the presence of sucrose, glucose or semicarbazide.

Dr. Nail also testified about 1968 and 1970 papers by Sanford Berman that point to the use of sucrose to increase the viability of micro-organisms in freeze-drying. *See* Sanford Berman, et al., *Freeze-drying Various Strains of* 16 Applied Microbiology 1779 (1968) and Sanford Berman, et al., *Freeze-drying various Attenuated Strains of* 7 Cryobiology 40 (1970).

Dr. Nail testified that from his work as a graduate student, he was aware of liposomes and their use as drug delivery vehicles. He also explained that liposomes are analogous to membrane structures, such as cells or microorganisms.

He looked to the articles cited above and others and concluded that in 1977 one skilled in the art of freeze-drying would have expected to need a protectant when freeze-drying a liposome and would have looked to sugars, particularly disaccharides, as the protectants. Dr. Nail testified that the 1972 Racker article establishes the use of sucrose to maintain the integrity of phospholipid vesicles after freeze-drying.

Vestar also offered the opinions of Dennis Chapman. Dr. Chapman is a professor of biophysical chemistry and head of the Department of Protein and Molecular Biology at the Royal Hospital School of Medicine in London. He received his Doctor of Science Degree from the University of London in 1966, where he studied phospholipids and biomembranes. He testified that between 1968 and 1980, the field of phospholipid membranes and liposomes was "considerably fashionable." Physical chemists, biophysicists, and cell biologists entered and worked in the field, as did scientists interested in drug delivery and oxidative phosphorylation. Dr. Chapman stated: "Everyone was talking to everybody about lipids and vesicles and liposomes and so on." He testified that during this period there was no standard nomenclature. The term "vesicles" was used up until 1978, when there was a plea to use a common language made at a New York Academy of Science meeting and people moved toward the use of the term liposome.

Dr. Chapman described his work with proteins in lipid membranes, including the incorporation of calcium into liposome systems, and the effects of cholesterol on the organization of lipids in liposome systems. He testified that through their research, he and his colleagues were able to show that there was an analogy between the behavior they were finding in the liposome system and in natural membranes, such as red blood cells, mycoplasma membraces and mitochondrial membranes. He testified that this early work was aimed at understanding the properties and behavior of natural biomembrane systems and the ways in which liposomes could be used as model membrane systems to provide insights into the properties of natural biomembranes.

Dr. Chapman described work in the late 1960s and early 1970s on the *in vivo* use of liposomes for replacing enzymes and as a potential drug carrier. He also testified to a May 1971 paper he wrote with Dr. D. Siminovitch entitled "Liposome Bilayer Model Systems of Freezing Living Cells" in which, in investigating freezing damage to cells, they compared liposome model systems with the freezing of cells. In the experiments described in that paper, Drs. Chapman and Siminovitch did not freeze-dry the liposomes and did not use cryoprotectants, as they intended to study damage produced in freezing.

Dr. Chapman testified that as early as 1965, polyvinyl pyrrolidone and sucrose in particular were known and used as cryo- and lyo-protectants. He offered his opinion that the method set forth in the claims of the Schneider patent was not new in 1977: liposomes were known, hydrophilic compounds

were known, the relationship between liposomes and the natural biomembranes and many of the protectants for the membranes was known, and the use of liposomes for *in vivo* drug delivery was known.

Dr. Chapman testified that the 1972 Racker article was pioneering in that it described for the first time the way in which a protein could be incorporated into the lipid bilayer structure of the liposomes. It also showed, as is reported in the summary printed at the beginning of the article, that "[t]he integrity of the cytochrome oxidase vesicles was retained after freeze-drying, provided sucrose was present during the process." Dr. Chapman testified that the term vesicle was another word for liposome and thus, the summary can be read as revealing that the integrity of the cytochrome oxidase liposomes was retained after freeze-drying, provided sucrose was present during the process. He offered his opinion that this summary describes exactly what is described by the words in the claims of the Schneider patent.

Dr. Chapman testified that respiratory control is a marker of the integrity of the vesicle. As described in the Racker article, the respiratory control value is the ratio of the rate of respiration in the presence and absence of an uncoupler.

To measure respiratory control, one needs a closed vessel, where protons, for example, are unable to rush into the system. Racker measured respiratory control by measuring the oxygen uptake which is associated with the electron flow going from the cytochrome *c* down to the cytochrome oxidase, setting up a protein gradient of hydrogen ions essentially being pumped out of the vesicle. The phospholipid bilayer membrane acts as an impermeable barrier, so that the protons can not easily leak back in. The respiratory control value as a marker of the integrity of the vesicle showed that if you go through the freeze-drying process without any sucrose, the vesicle opened up. Thus, Racker was showing that the presence of the sucrose retains the integrity of his liposome.

Dr. Chapman testified that respiratory control is not a measure of enzyme activity, as enzyme activity can occur, but without a closed liposome, you will not have a proton gradient and not be able to measure respiratory control. He testified that Racker was using the respiratory control value as a marker of integrity of the vesicle and showed that if you perform the freeze-drying process without any sucrose, the vesicle will open up. On the other hand, when Racker added sucrose in the freeze-drying process, one finds good respiratory control. That is, the presence of sucrose retains the integrity of the liposome. Thus, Dr. Racker reported in his article, "inclusion of sucrose during lyophilization protected against the loss of respiratory control."

Dr. Chapman also offered his opinion on the accuracy of certain statements in TLC's August, 1991 Amendment and Response to the PTO (Def. Ex. 772), which form the basis of Vestar's claim that the patent is unenforceable due to inequitable conduct on the part of TLC. Those statements and Dr. Chapman's opinions are as follows:

1. Statement at page 10: "Neither Racker nor Sreter recognized or addressed the problem solved by the present invention."

Chapman's opinion is that this statement is not accurate, as Racker shows in his paper that you have to have sucrose present to obtain vesicle integrity.

2. Statement at page 11: "The only real information provided by Racker is that the higher the respiratory control, the better the cytochrome oxidase vesicle is for studying the enzyme."

Chapman's opinion is that in the context of lyophilized freeze-dried preparation this statement does not make sense. The respiratory control values are a marker for the integrity of the vesicle. Enzymatic activity is required to retain control, but respiratory control requires, in addition, a closed vesicle; thus, you can have enzymatic activity without respiratory control.

3. Statement at page 11: "Moreover, Racker did not measure or study any parameter or provide information that would be important for the preparation, processing or evaluation of liposomes, much less liposomes that are suitable for administration *in vivo; e.g.*, parameters such as encapsulation efficiency, size and size distribution, leakiness, etc."

Chapman's opinion is that the statement is inaccurate in that Racker does describe the preparation, processing, and size distribution, all of which are relevant to the use of liposomes *in vivo*.

4. Statement at page 13: "At the outset, Racker's reported results do *not* indicate that sucrose is important in recovering vesicles."

Chapman's opinion is that this statement is not accurate; Racker discusses the use of sucrose and indicates it's importance in retaining the integrity of the vesicle.

5. Statement at page 13: "According to Racker, the ability to measure enzyme activity at all indicates the recovery of vesicles, *even when sucrose was absent during lyophilization.*"

Chapman's opinion is that this statement is not accurate. Racker reported that he

could measure enzymatic activity of the vesicle when it is dried down without sucrose, but he could not report that he was able to lyophilize the vesicles and recover them and retain respiratory control without using sucrose.

6. Statement at page 13: "Racker's sole observation was the maintenance of respiratory control in the cytochrome oxidase vesicles lyophilized in the presence of sucrose."

Chapman's opinion is that Racker also showed that the integrity of the vesicle is retained when it is lyophilized in the presence of sucrose. Racker further indicates that the damage, when sucrose is absent, is due to a physical damage to the phospholipid bilayer.

7. Statement at page 13: "As explained above, respiratory control is solely a measure of enzyme activity, and has nothing to do with the stability of liposomes.

Chapman's opinion is that this statement is totally incorrect, as respiratory control is not just a measure of enzyme activity. At trial, Chapman testified: "I know it's totally, completely wrong. I find it surprising to see that statement."

8. Statement at page 17: "According to Racker, intact vesicles which retain the cytochrome oxidase are recovered whether or not sucrose is used in the lyophilization process."

Chapman's opinion is that this statement is completely erroneous and goes against the statements in the paper.

9. Statement at page 19: "The present invention relates to a method of dehydrating liposomes so that, upon reconstitution, a liposome dispersion suitable for use as an *in vivo* delivery system is recovered. In sharp contrast, the field of endeavor of Racker and Sreter was studying membrane enzymes *in vitro*. In the minds of those skilled in the art at the time of the filing date of the present patent, these two areas were separate and distinct so that an investigator faced with the problem of reconstituting dehydrated liposomes useful as *in vivo* delivery systems would not have turned to enzymologists for assistance or guidance. Perhaps the most powerful evidence in support of this conclusion is provided by the Racker article. The result of a Science Citation Index search of the Racker article (annexed hereto) reveals that Racker was cited by the authors of at least 128 scientific publications. As is evident from the titles, every one of those 128 articles relates to enzymes and enzyme activity, including the 63 articles published in the same year as the filing date of the present patent. Not even one of the 128 titles mentions liposomes as delivery systems for *in vivo* applications."

Chapman's opinion is that regardless of the truth of this statement, Racker's work was immediately picked up as far as the detergent dialysis method of including membrane proteins in lipid systems, and that Racker was not outside the field of endeavor of the Schneider patent.

TLC called Dr. Cullis to testify on these issues. As noted above, Dr. Cullis earned a Ph.D. in physics from the University of British Columbia in 1972. In 1973 he began to study the biophysics of membrane systems employing liposomes. At about that time he also initiated work on the reconstitution of membrane proteins. He is a former president of a Liposome Company subsidiary and is now a Professor of Chemistry at the University of British Columbia.

Dr. Cullis testified that in 1977 the field of liposomes was divided into three groups of scientists: liposomologists who were interested in liposomes as drug-delivery vehicles; a more established group looking at biophysical properties of lipids (of which he was a member); and a third group, enzymologists or bioenergists, who were interested in reconstituting certain proteins in vesicles to study the functional properties of the proteins. Cullis testified that the communication among these three groups was not good and that at that time, liposomologists would not have read Racker. This is because they would not have understood his measurement of respiratory control and would not have been as interested in the function of proteins and enzymatic measurements.

Dr. Cullis reviewed the Racker article and noted that Racker was a leader in solving the problem of how to get protein (specifically, cytochrome oxidase) out of a membrane and into a vesicle, in order to study it. Racker did this with a detergent, cholate. He added the detergent to the mitochondrial membrane where the cytochrome oxidase enzyme is found. He dissolved that membrane to form micelles and then reconstituted the cytochrome oxidase into vesicles, where the cytochrome oxidase is located in the membrane of these vesicles.

Dr. Cullis offered his opinion that the cytochrome oxidase vesicles Racker used in the freeze-drying experiment were leaky vesicles and would not be suitable for *in vivo* use as drug delivery vesicles as the material would leak out. He also offered the opinion that the 1972 Racker article disclosed that the use of more cholate improved respiratory control. He testified that Racker's results relate to the activity of an enzyme in a

reconstituted vesicle and do not have any relation to liposomes for drug delivery.

B. *Is the '360 Patent Invalid as Anticipated by Racker*?

Vestar contends that the Schneider patent is invalid under 35 U.S.C. § 102(b). That statute reads:

§ 102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless—

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States. . . .

Vestar argues the Racker article teaches that liposomes are inherently suitable for *in vivo* use and that they can be lyophilized and rehydrated while maintaining structural integrity, provided sucrose is present during lyophilization, and thus describes each of the steps and elements of claims 1-4 and 11-14 of the patent. It argues that the invention was, therefore, described in the Racker article and the patent is invalid under 35 U.S.C. § 102(b).

TLC responds by arguing Vestar cannot show that each and every element of the claims is found in Racker. First, the article does not disclose the recovery of liposomes suitable for use *in vivo*. Second, there is no evidence in the article that the original vesicles are recovered. Third, the cytochrome oxidase vesicles are not liposomes. Fourth, the article does not disclose the formation of a stable powder. Finally, it does not disclose the weight ratios of hydrophilic compound to lipid required in claims 3, 4, 13 and 14.

[2] The court finds the 1972 Racker article does use the term vesicle to describe what is now called a liposome. In addition, it discloses the use of sucrose to preserve the integrity of liposomes when they are freeze-dried. However, it does not appear that Racker's use of the detergent cholate would have been consistent with *in vivo* uses of the vesicles. Thus it would appear that the 1972 Racker article does not disclose the limitation of *in vivo* use which appears in the claims of Schneider's patent. The court finds, therefore, that Vestar has failed to show by clear and convincing evidence that the Racker article discloses each and every element in the claims of the Schneider patent. That is, Vestar has failed to prove that Racker anticipates the claims of the Schneider patent.

C. *Is the '360 Patent Invalid as Obvious in View of the Prior Art*?

Vestar contends the Schneider patent is invalid under 35 U.S.C. § 103, which reads:

§ 103. Conditions for patentability; non-obvious subject matter

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In deciding whether the subject matter of the Schneider patent would have been obvious, the court must (1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims at issue; and (3) resolve the level of ordinary skill in the pertinent art. Against this background, the court looks to other facts that may tend to make it more probable than not that the subject matter of the invention would have been obvious, including whether there was a long-felt and unsolved need for the subject of the patented invention, whether others had tried and failed to meet that need, and the commercial success of the patented invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 [148 USPQ 459] (1966). For prior art to render the invention of a patent obvious, the art must suggest the invention and provide one of ordinary skill in the art with a reasonable expectation of success based on the teachings of the art.

1. *The field of invention and the level of ordinary skill in the art*

The claims of the Schneider patent are directed to a process for the dehydration of a colloidal dispersion of liposomes, with a preferred method of dehydration being freeze-drying. Vestar contends that the pertinent art is the art of dehydration with particular emphasis on dehydration by lyophilization. Vestar argues that prior to August 5, 1977, the effective filing date of the patent, a person of ordinary skill in the art of dehydration by lyophilization would have had at least a bachelor's degree in chemistry or a closely related field.

TLC contends that correct field of the invention of the '360 patent is the storage of drug-containing liposomes to maintain them in a stable form for an extended period of time so that they can be recovered and used *in vivo*, and that in the '360 patent the problem of long-term storage is solved by dehydrating a mixture of liposomes and a hydrophilic compound. Consistent with its

view on the field of the invention, TLC contends that a person skilled in the art is one with an advanced degree in chemistry or biochemistry and most importantly, one who has had considerable experience with and understands the nature of liposomes.

[3] While the parties have approached this issue as a question of the field of invention, their disagreement really relates to the nature and breadth of skills expected from a person in a particular field — in other words, the level of skill the court imputes to one of ordinary skill in the art. In this case, the court finds that one of ordinary skill in the art is one who has been described during the litigation as a liposomologist, in contrast to an enzymologist, biophysicists, or cell biologist, and not necessarily a person skilled in dehydration. It appears from the record that in 1977, a liposomologist would have a graduate degree in chemistry or biochemistry, and would be experienced with liposomes, perhaps in the use of liposomes for the delivery of drugs.

2. *Scope and content of the prior art*

In *Graham*, the Supreme Court's decision with respect to the patent at issue in *Calmar, Inc. v. Cook Chemical Co.* suggests that the court's inquiry should be directed to the problem confronting the inventor, art pertinent to that problem, and the reasonable level of insight we expect that inventor to have into that pertinent art. The Court noted: "The problems confronting [the inventor] and the insecticide industry were not insecticide problems; they were mechanical closure problems. Closure devices in such a closely related art as pouring spouts for liquid containers are at the very least pertinent references." *Graham*, 383 U.S. at 35. Thus, the scope and content of the prior art includes references from those areas a person with ordinary skill in the art would look to in solving a particular problem. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 [230 USPQ 416] (Fed. Cir. 1986), *cert. denied*, 484 U.S. 823 (1987); *Ryko Mfg. Co. v. Nu-Star Inc.*, 950 F.2d 714, 719 [21 USPQ2d 1053] (Fed. Cir. 1991); *see generally*, 2 Donald S. Chisum, *Patents*, § 5.03 [1], at 5-79 (1994). In this case, the problem confronting Schneider was storing liposomes and not merely the creation of liposomes.

Vestar's claim that Schneider's invention or solution to this storage problem was obvious raises two questions. The first is whether references in the art of lyophilization, and lyophilization of cells, are pertinent to the problem of storing liposomes. If they are, the second question is what level of insight should a liposomologist be expected to have in these fields, and to what extent should we expect a liposomologist to examine references in these fields for the purpose of solving this problem.

[4] In this context the court credits the testimony and opinions of Dr. Nail and finds that in 1977 and before, one of ordinary skill in the art of freeze-drying science and technology would be expected to know about the need for protective agents and what kinds of compounds would be effective in protecting cells and microorganisms during freeze-drying. Further, the court finds these matters were not so difficult or complex that a liposomologist who looked to the science of freeze-drying to assist him in working to solve a problem with liposomes could not be expected to find this information reasonably available to him at that time. Thus, the court finds that such a person skilled in the art of liposomes in 1977 and before, who approached research using lyophilization, would be expected to have educated himself or herself sufficiently to have been familiar with the use of protectants such as sucrose in the freeze-drying of certain objects (such as cells).

Further, the court credits the testimony and opinions of Dr. Chapman, and finds that liposomologists did look to liposomes as model cells. The court also finds that a liposomologist skilled in that art before 1977 and before should be expected to be generally familiar with references in the allied fields of enzymology and cell biology, at least to the extent that they were directed to the study of cells, vesicles, and liposomes. Consequently, they would be generally familiar with work showing efforts to freeze cells, use of lyoprotectants and cryoprotectants during freezing and freeze-drying of those cells or liposomes, and with Racker's article, at least to the extent that he described the use of sucrose as a protectant during lyophilization of liposomes.

Dr. Cullis' background and career provide a good illustration of how those working with liposomes draw from skills in the art to integrate knowledge from related fields. He earned a doctorate in physics. In 1972 or 1973, he moved from physics to biophysics, where he studied membrane systems. In 1982, he moved to the field known as liposomology and at the same time, began work on the reconstitution of membrane proteins. At trial, he demonstrated sufficient familiarity with dehydration to offer opinions on lyophilization and the use of protectants. Similarly, Dr. Chapman began studying phospholipid and biomembranes in 1963, engaged in research on the use of proteins in lipid membranes, published articles on freezing lipo-

somes, knew Racker for his work with incorporating protein membrane into liposomes, and was familiar with liposomologists who worked on using liposomes as drug carriers.

3. *Differences between the prior art and the claims at issue*

Vestar relies on the testimony of Drs. Nail and Chapman, and the papers they testified to during trial, to support its position that prior to August 5, 1977, lyophilization was a well-known technology; that microorganisms (single-celled living entities) had been freeze-dried and sold commercially in dehydrated form; and that it was well known that sucrose, other mono- and disaccharides, albumin, and polyvinyl pyrrolidone worked as protectants during freeze-drying. Vestar also relies on the testimony of Nail and Chapman to confirm that prior to August 5, 1977, the analogy of liposomes to cells was widely recognized, as liposomes had been used extensively as models of cell membranes.

TLC responds by arguing that Vestar's arguments on obviousness, and Dr. Nail's and Dr. Chapman's opinions, are based on a combination of prior art references that are not analogous to Schneider's invention. TLC contends that references (like Siminovitch) that speak to freezing liposomes do not relate to lyophilization and would not have been consulted by a hypothetical skilled worker in the field of lyophilization. Similarly, TLC contends that cells are not analogous to liposomes and that results achieved from freezing or drying cells cannot be extrapolated to liposomes. TLC also argues that the study of enzyme activity was remote from the field of drug delivery, because, for example, the components relied on by Racker, including a detergent, would be unsuitable for drug delivery purposes.

The court is not persuaded by TLC's arguments. The articles on freezing liposomes may not be directly relevant to lyophilizing liposomes, but they provide information useful in solving the problem of freeze-drying liposomes. For example, the articles show scientists were freezing cells, and scientists understood that liposomes were analogous to living cells. In 1971 Siminovitch and Chapman wrote: "An analogy in terms of osmotic and permeability behaviour to living cells has been demonstrated with the multi-bilayer system of liposomes studied by Bangham and co-workers." D. Siminovitch & D. Chapman, *Liposome Bilayer Model Systems of Freezing Living Cells*, 16 FEBS Letters 207 (1971). Because of the analogy between cells and liposomes, one skilled in the art would consider problems and solutions in the lyophilizing of cells as relevant to the lyophilizing of liposomes.

It is also correct that certain of the components used by the enzymologist, such as the detergents, might not have been appropriate for *in vivo* use. That does not mean, however, that liposomologists cannot learn from enzymologist's work with liposomes. One audience may read Racker for his work in measuring enzyme activity. Another audience may read his work for his lyophilization of liposomes. To the latter, and particularly those who had an interest in freezing or freeze-drying liposomes as drug delivery vehicles, it would not be particularly relevant to them that Racker used a detergent to purify the enzyme he placed in the liposome. However, other parts of Racker might be highly relevant to problems they faced.

Based on Dr. Nail's testimony and the papers he relied on in offering his testimony, including Vladimir Damjanovic & Draginja Radulovic, *Survival of Lactobacillus Bifudus After Freeze-Drying*, 4 Cryobiology 30 (1967), the court finds that before 1977, it was well known in the field of freeze-drying that a sugar such as sucrose would preserve the integrity of cells during freeze-drying. Other articles that support his opinions include Hiroyuki Yugi et al., *Freeze Drying of Mycoplasma*, 10 Cryobiology 464 (1973) and Margaret C. Norman et al., *Preservation of Mycoplasma Strains by Freezing in Liquid Nitrogen and by Lyophilization with Sucrose*, 20 Applied Microbiology 69 (1970).

In addition, based on Dr. Chapman's testimony and the papers he relied on in offering his testimony, including D. Siminovitch & D. Chapman, *Liposome Bilayer Model Systems of Freezing Living Cells*, 16 FEBS Letters 207 (1971), the court finds that prior to 1977, liposomologists, or those who worked in the field of liposomes, understood that the similarities between liposomes and cells are such that liposomes were used as models of cell membranes. Further, while there are differences between cells and liposomes, there is nothing about those differences that would have led a liposomologist to assume that the success in using protectants to lyophilize cells would not lead, by analogy, to success in using protectants to lyophilize liposomes.

Based on these opinions, the court finds that before 1977 one skilled in the field of lyophilization would have expected that a sugar such as sucrose would preserve the integrity of liposomes during freeze-drying. The 1972 Racker article confirms this conclusion. In the article, Racker describes adding sucrose to his liposome suspension to

avoid freeze-drying damage, stating: "The integrity of the cytochrome oxidase vesicles was retained after freeze-drying, provided sucrose was present during the process."

4. *Other evidence relevant to obviousness*

Neither party has offered substantial evidence on other facts the court might look to in evaluating whether this invention would have been obvious to one skilled in the art at the time. TLC reports there was a long-felt need for any type of long-term storage of drug delivery liposomes, but there is little evidence of that need beyond Vestar's introduction of AmBisome in 1989. Similarly, TLC argues that Vestar's sales of AmBisome are evidence of commercial success of the process described in the patent. These facts are not particularly compelling.

One fact TLC identified during reexamination is significant. That is, TLC's 1991 search of articles citing the 1972 Racker article showed that it was cited in over 128 articles and not one of those articles mentioned liposomes as delivery systems for *in vivo* applications. TLC argues this information suggests that it is incorrect to include Racker's work (and perhaps the work of other enzymologists) within the field of art the hypothetical liposomologist would have been expected to examine at the date of the invention. However, the meaning of TLC's search results is far from clear. It could be, as Dr. Chapman has suggested, that the change in terminology from vesicles to liposomes meant Racker's article was overlooked. On the other hand, it could be that Racker's work was seen as significant, but only by those interested in enzymes.

Neither party sought to follow up on this point by offering evidence on the content and focus of those articles that did cite Racker. Consequently, the court is inclined to find TLC's report on its survey of some relevance, but not sufficiently probative to overcome the relevance of the findings Racker reported and the other evidence that tends to show one of ordinary skill in the art of liposomology would have been aware of and examined work enzymologists were doing with liposomes or vesicles, as they were called at that time.

5. *Conclusion as to obviousness*

In conclusion, the court finds Vestar has shown by clear and convincing evidence that the subject matter of the '360 patent would have been obvious to one of ordinary skill in the art at the time the invention was made. The prior art suggested the invention and provided one of ordinary skill in the art with a reasonable expectation of success based on the teachings of the art.

D. *Is the '360 Patent Invalid as not Enabled or Indefinite?*

Vestar contends the Schneider patent is invalid under 35 U.S.C. §112 as not enabled and as indefinite. That section reads, in part, as follows:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

To determine whether a claim is indefinite, the court looks to whether one of skill in the art, after reviewing the claims and the specification, would understand what is being claimed. *Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 826 [221 USPQ 568] (Fed. Cir. 1984).

Vestar argues that the term "hydrophilic compound" as used in the patent is extraordinarily broad and that Schneider gives no guidance to determine which compounds to use beyond the six he refers to in the patent. It contends Schneider's failure to be more specific renders the patent invalid as indefinite and as lacking enablement, as an experimenter would receive no guidance as to how to identify which compound would work.

TLC has responded by arguing that Schneider gave the term "hydrophilic compound" a special meaning by stating: "Therefore, said hydrophilic compound is actually a stabilizing additive which protects the liposomes of the dehydrated product and keeps them in a condition suitable for further use." TLC further argues that an experimenter of ordinary skill in the art would not have to go outside the four corners of the patent to select any one of several hydrophilic compounds that work in the invention.

[5] The court agrees with TLC that Schneider's identification of hydrophilic compounds are sufficiently specific to put one skilled in the art on notice as to what compounds Schneider found suitable. Consequently, the court rejects Vestar's claim that the patent is invalid as indefinite or for lack of enablement.

E. *Is the '360 Patent Unenforceable Because of The Liposome Company's Statements to the Patent Office on the Racker Article?*

Vestar has counterclaimed for a judgment that the Schneider patent is unenforceable because TLC misled the PTO by making material misstatements and misrepresentations concerning the 1972 Racker article during reexamination. Vestar contends TLC made these misrepresentations with the intent that the PTO would rely on them in granting the Reexamination Certificate.

An applicant for a patent has an uncompromising duty to report all facts affecting patentability of the claimed invention to the PTO in order to assure that "patent monopolies spring from backgrounds free from fraud or other inequitable conduct." *Precision Instrument Mfg. Co v. Automotive Maintenance Mach. Co.*, 324 U.S. 806, 816-18 [65 USPQ 133] (1945). A claim of inequitable conduct requires proof, by clear and convincing evidence, of the failure to disclose material information or the submission of false material information to the PTO with an intent to mislead. *Kingsdown Medical Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 872 [9 USPQ2d 1384] (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1067 (1989). Vestar's claim contains the following three elements: 1) TLC misstated or omitted to state to the PTO; 2) a material fact; 3) with the intent to mislead to PTO.

Facts or information are material in this context if there is a substantial likelihood that a reasonable examiner would consider the information pertinent in deciding whether a patent should issue. *J.P. Stevens & Co., Inc. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1559 [223 USPQ 1089] (Fed. Cir. 1984), *cert. denied*, 474 U.S. 822 (1985). The PTO granted reexamination of the patent in response to TLC's petition which was based on Racker. For this reason, no one has argued that the Racker article was not material.

Counsel have spent some time and energy on whether or not, in attempting to distinguish it from the patented invention, TLC misrepresented or misdescribed Racker to the Patent Office. The court is inclined to agree with Vestar, and Dr. Chapman's testimony, that TLC did misdescribe Racker. Thus, for example, the following two statements by TLC to the PTO seem to be inaccurate characterizations of what Racker reports: "The only real information provided by Racker is that the higher the respiratory control, the better the cyto-chrome oxidase vesicle is for studying the enzyme" and "According to Racker, intact vesicles which retain the cytochrome oxidase are recovered whether or not sucrose is used in the lyophilization process." However, most of the misstatements Vestar has identified tend to be more confusing than blatantly wrong, and are more in the nature of argument than description or misrepresentation, such as the statement that "[n]either Racker nor Sreter recognized or addressed the problems solved by the present invention."

[6] TLC's mischaracterization or misdescription of Racker is not however, a material misstatement of fact. TLC disclosed the material facts to the PTO, including Racker's article. Since TLC disclosed the existence of Racker to the PTO, and the article was available to the examiner to be read and evaluated, TLC's mischaracterization of Racker's experiments and findings, and its misleading arguments on the article's significance, were not misrepresentations of fact and did not breach any duty of candor TLC owed the Patent Office.

This problem presented by the Racker article is an example of a difficult situation the examiners face in an *ex parte* proceeding. He or she may have the material facts on hand, but may not have the time or information to appreciate exactly their significance. While lawyers have a duty of candor to disclose material facts to an examiner, that duty does not stretch so far that it should inhibit a lawyer from making an argument to the examiner on how he or she should view those facts.

In this case, TLC put the material facts in front of the examiner, but then misstated how they should be read. The court finds Vestar has failed to show, however, that TLC intended to mislead that PTO. To the extent TLC did in fact mislead the PTO, it was with inaccurate arguments rather than with material misstatements of fact. In this case, it simply appears that without the benefit of more information, and more advocacy, the examiner failed to appreciate the significance of the Racker article.

For these reasons, the court will deny Vestar's claim for a declaratory judgment that the '360 patent is invalid because of TLC's statements to the Patent Office during the reexamination.

The court will issue an Order in accordance with this Opinion.

U.S. District Court
Eastern District of Michigan

Indian Head Industries Inc. v. Ted Smith Equipment Co.

No. 92-CV-74367